REVIEW ARTICLE

Relationship of age-specific incidence rates to immunological aspects of Hashimoto's thyroiditis

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Summary: Studies of the age-specific incidence rates of the appearance of Hashimoto's thyroiditis indicate that this disorder appears at random in a genetically preselected population. Following an initial lag in the first few years of life, the disease appears at a constant rate thereafter in this population.

The age-specific incidence rates were similar to those previously reported for Graves' disease. Moreover, there is considerable evidence implicating cell-mediated immunity in both diseases, with the likelihood of cooperating humoral antibodies as well. It may be hypothesized that the two diseases are primarily due to genetic defects in immunological surveillance, which result in an inability to destroy or control a specific forbidden clone of thymic-derived lymphocytes which may arise by normal random mutation.
The T-lymphocyte interacts with its complementary antigen (on a hitherto normal thyroid cell), setting up a cell-mediated immune response; in addition it may cooperate with bursa-equivalent lymphocytes, which then produce humoral antibodies.
It is possible that both cell-mediated immunity and humoral antibodies are necessary for the full expression of the disease.

Résumé: *Relation entre les taux de morbidité liée à l'âge et les facteurs immunologiques de la thyroïdite de Hashimoto*

L'étude des fréquences, spécifiques de l'âge, d'apparition de la maladie de Hashimoto indique clairement que cette affection apparait au hasard dans une population donnée, prédéterminée sur le plan génétique. Après un décalage initial durant les quelques premières années de la vie, la maladie fait ensuite son apparition à un rythme constant au sein de ladite population.

Les fréquences, spécifiques de l'âge, sont voisines de celles déjà rapportées dans la maladie de Graves. Par ailleurs, on possède une foule de preuves que l'immunité à médiation cellulaire joue un rôle dans les deux pathologies. En outre, il est probable que les anticorps humoraux s'associent à cette action. Il est possible de soutenir l'hypothèse que les deux pathologies relèvent essentiellement de tares génétiques dans la mémoire immunologique, lesquelles se traduisent par l'impossibilité de détruire (ou du moins d'enrayer) un clone de lymphocytes thymo-dépendants qui peuvent survenir par une mutation normale due au hasard. Le lymphocyte-T réagit réciproquement avec son antigène complémentaire (sur une cellule jusque là normale), déclenchant une réaction immunitaire à médiation cellulaire. Il peut en outre collaborer avec les lymphocytes bursa-equivalent qui produisent des anticorps humoraux.
Il est possible que les deux facteurs, soit l'immunité à médiation cellulaire et les anticorps humoraux, soient essentiels à la manifestation de la pathologie dans toute son intégralité.

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It is now generally accepted that Hashimoto's thyroiditis is an autoimmune disorder.[1] A decade ago it was believed that thyroglobulin leakage from its sequestered location within the follicle into the interstices, where it was recognized as "non-self" by the reticuloendothelial system, initiated Hashimoto's thyroiditis.[2] This view is no longer tenable. Excessive thyroglobulin leakage, as in subacute thyroiditis, does not usually lead to Hashimoto's disease.[3] Moreover, thyroglobulin is normally present in the human circulation, including cord blood,[4] which is strong evidence against the "secluded antigen" theory of causation of this disorder. In fact, there is no evidence that there is any antigenic change within the thyroid gland in Hashimoto's thyroiditis.[5]

While circulating thyroid autoantibodies are found in virtually all cases of Hashimoto's thyroiditis, there is little evidence that these humoral immunoglobulins are important in inducing the thyroid lesions.[1] Although thyroid cells in tissue culture may be damaged by humoral "cytotoxic factor" which is closely related, if not identical, to the thyroid microsomal antibody,[6,7] the passive transfer *in vivo* of thyroid antibodies from patients with Hashimoto's thyroiditis to Rhesus monkeys does not produce lesions in the thyroid glands of the recipients.[8] The suggestion that passive transfer of thyroid autoantibodies across the placenta might be responsible for cretinism[9] has not been confirmed[10] and the incidence of cretinism is not increased in infants born to mothers suffering from Hashimoto's disease.[11]

While humoral antibodies have been virtually ruled out as a major factor in the genesis of the thyroid lesions, there is now considerable evidence indicating that a cell-mediated immune

mechanism (delayed hypersensitivity) is of primary importance. Firstly, the transfer of lymphocytes from animals with experimentally-induced thyroiditis to other animals has been shown to produce thyroiditis in the recipients.[12-14] Secondly, lymphocytes from patients with Hashimoto's thyroiditis induce thyroid cell damage and reduced function in tissue culture,[15] and the same is true for lymphocytes from animals with experimental thyroiditis.[16] Similarly, lymphocytes from patients with Hashimoto's disease are cytotoxic to heterologous tumour cells coated with human thyroid antigens.[17] Furthermore, lymphocytes from patients with Hashimoto's disease will show migration inhibition factor when exposed to thyroid antigens,[18-20] and will undergo blast transformation under similar circumstances.[21,22] Finally, the proportion and absolute numbers of thymic-derived lymphocytes is markedly increased in the peripheral blood of patients with this disorder.[23] Thus, cell-mediated immunity (a function of thymic-derived lymphocytes) would seem to be well established in Hashimoto's disease. Cell-mediated immunity has also been demonstrated by similar tests in Graves' disease[18,23-26] although there is little evidence that the lymphocytes in the latter disorder are cytotoxic.[27,28] It is clear that Graves' disease and Hashimoto's disease share a common genetic predisposition, occur in the same families,[29] and may even coexist within the same thyroid gland.[30] Furthermore, both often coexist with other possibly autoimmune diseases, e.g. pernicious anemia, Addison's disease, diabetes mellitus, myasthenia gravis, rheumatoid arthritis and vitiligo.[31]

In 1963, Burch and Rowell[32] reported mathematical evidence (based on age-specific incidence rates) to support the opinion that Hashimoto's thyroiditis occurs at a random rate in a genetically predisposed population. Furthermore, since Hashimoto's thyroiditis has a relatively high incidence in females, Burch and Rowell thought there would be a central role for the X chromosome in this genetic predisposition. The comparative rarity of this disorder and its high penetrance (almost all of the population at risk develops the disease within the normal lifespan) make it possible that this population is characterized, at least in part, by functionally dominant genes on the X chromosome. On the basis of the statistics cited by these authors, the most obvious interpretation was that individuals in this subpopulation inherit dominant mutant genes on the X chromosome. Therefore, females have at least twice the chance of having the genetic defect. If several genetic defects are necessary for the production of the disease, this ratio can be even higher.

It should be emphasized that the age-specific incidence rates of the appearance of the disease in the population actually relate the number of cases of the disease appearing in each decade of life to the total population of the same age group. When not all of the cases in the disease group within a given area are known, one can still derive a relative age-specific incidence rate by dividing the proportion of cases of the disease appearing in each decade of life by the proportion of the population in that same age decade living in the study area.

Table I—Age-specific incidence rates of Hashimoto's disease

	Age (years)	Ontario population		Cases of Hashimoto's disease		
		Number	% of total population	Number	% of total	dN/dT*
Males	0-9	775,791	21.67	0	0	0
	10-19	656,534	18.34	3	10.3	0.561
	20-29	556,088	15.54	4	13.8	0.888
	30-39	466,243	13.03	6	20.6	1.581
	40-49	428,440	11.97	8	27.5	2.297
	50-59	326,072	9.11	5	17.2	1.888
	60-69	212,790	5.95	2	6.9	1.159
	> 70	157,011	4.39	1	3.6	0.820
		3,578,969	100	29	100	
Females	0-9	739,834	21.25	0	0	0
	10-19	630,933	18.12	11	9.5	0.524
	20-29	462,821	13.29	15	12.9	0.970
	30-39	453,528	13.03	21	18.1	1.389
	40-49	431,901	12.40	34	29.3	2.363
	50-59	320,655	9.21	26	22.4	2.432
	60-69	230,544	6.62	6	5.2	0.785
	> 70	211,505	6.08	3	2.6	0.427
		3,481,721	100	116	100	

An assumption is made that the distribution of the population with respect to age and sex is the same in the area from which these patients were derived as in the entire province of Ontario, which the figures in column 2 represent.
*dN/dT refers to the age-specific incidence rate, which herein is expressed as column 5 divided by column 3.

Methods and materials

We have reviewed data for the age-specific incidence rates[32] based on 145 cases of "classical" Hashimoto's thyroiditis (116 females, 29 males). The diagnosis in each case was suggested by a very firm, often lobulated thyroid enlargement, and by the presence of thyroid autoantibodies in titres above 1:2000 for the tanned erythrocyte agglutination test (for antithyroglobulin[33]) and/or 2+ for the complement fixation test (for the antibody against thyroid microsomes[34]). In 46 patients the diagnosis was substantiated by needle biopsy. In 93 patients there was clinical and/or biochemical evidence of hypothyroidism. These cases were obtained from our clinical records for the period 1959 to 1969. The proportion of cases of the disease appearing in each decade of life was then related to the proportion of the total population of Ontario (1966 census[35]) for each decade age-group. Since our cases did not represent most of the patients with Hashimoto's disease in Toronto, let alone Ontario, it was possible to derive only a relative, rather than an absolute, age-specific incidence rate.

Results

The results are shown in Table I and Fig. 1. There is an initial lag interval before any cases appear. Thereafter there is a continuing increase in the age-specific incidence rate until a peak is reached in the sixth decade. This is followed by a sharp decrease, approaching but not reaching zero. The curves are somewhat broader for the male group, perhaps because the sample (29 patients) was so small. We might have anticipated similar curves for both sexes had there been adequate sampling.

Discussion

There is already considerable evidence that genetic factors are important in Hashimoto's disease. There are numerous reports of concentrations of Hashimoto's thyroiditis within families,[29,31] and the disease has been reported in identical twins.[36-39] In fact, in certain identical twins Hashimoto's thyroiditis has occurred in one twin and Graves' disease in the other.[40,41] Furthermore, thyroid autoantibodies are found in approximately 50% of asymptomatic relatives of patients with Hashimoto's disease.[42]

Curves for age-specific incidence rates in Hashimoto's disease and various other disorders (similar in general nature to those observed in our group of patients with Hashimoto's disease) have been analysed by Burch and

Rowell,[32] and Burch has written extensively about these rates.[43-45] In nonmathematical terms, the meaning of the data for Hashimoto's thyroiditis, as documented above, is as follows: If at birth a subpopulation is at special risk, through inheritance, of development of this disorder, then as this subpopulation ages, more and more members will succumb to the disease. If the probability of onset of the disease increases rapidly with age, the proportion of predisposed members who have not succumbed to it will decrease rapidly with age. When this proportion becomes small enough, the age-specific incidence rate, expressed with respect to the general population, will fail to increase with age. Consequently, a peak in the age-specific incidence rate will be attained, and this will then be followed by a decreasing incidence with increasing age. Theoretically, when every member of the predisposed population has finally been affected, the age-specific incidence rate should fall to zero.

Therefore the etiology of Hashimoto's thyroiditis would appear to conform to the following conditions as suggested by Burch and Rowell[32] and later by Burch:[43-45]

1. The disease is restricted to a genetic subpopulation.
2. The onset of the disease requires the accumulation in a carrier individual of at least two discrete changes (to account for the lag before cases appear in early life).
3. These discrete changes or events are random in character, and their average probability of occurrence is constant with respect to time (somatic mutation is a perfect example of such events).
4. The penetrance of the inherited tendency to the disease approaches unity within one lifespan.
5. The average age-specific mortality rates are the same in the general population and in the carrier subpopulation before the onset of the autoimmune disease.

The age-specific incidence rates that have been obtained from the patients in Toronto are somewhat different from those reported by Burch and Rowell[32] in patients with Hashimoto's thyroiditis in Leeds, England, although the above statements would apply to both sets of data. It is of further interest that we have also obtained data for age-specific incidence rates for Graves' disease in Toronto;[26,46] these are similar to those obtained from patients with Hashimoto's disease observed in the same locale. While the possibility of geographic factors in the pathogenesis of these disorders cannot be excluded, there is also a possibility that the selection of patients with Hashimoto's disease may have differed in Toronto as compared with Leeds.

Relationship of the age-specific incidence rates to the immunologic data

The evidence cited above indicates that the disorder in Hashimoto's thyroiditis results from cell-mediated immune reactions induced by specific thymic-derived lymphocytes within the thyroid gland interacting with thyroid follicular cells. Furthermore, it has been noted that there is no evidence indicating that an antigenic stimulus is necessary for the appearance of these lymphocytes.[26] The genetic observations and the results of study of the age-specific incidence rates indicate that the disease is occurring at random in a genetically predisposed population.

Since there is little, if any, evidence that an antigenic stimulus is a *sine qua non* in initiating the disorder, there is at least an equal likelihood that Hashimoto's disease represents a specific inherited defect in immunological surveillance. Based on the clonal selection theory of Burnet[47-50] and Burnet and MacKay[51] as well as the suggestions of Burch and Rowell,[32] there may be an inherited defect in the elimination of a specific clone (a population of cells derived from the asexual division of a single cell) or a group of closely related clones of immunologically competent cells or lymphocytes. It may well be that "forbidden" clones of immunologically competent cells are arising at random normally in every person throughout life.[54] Forbidden clones are those directed against normal self constituents.

Such forbidden clones are controlled or eliminated as soon as they arise in normal persons as a result of immunological surveillance, itself a function of thymic-derived lymphocytes.[54] However, if a person has inherited a defect in immunological surveillance of a specific forbidden clone of thymic-derived lymphocytes (for example, having specificity for interaction with thyroid cells), and if this particular clone chanced to arise by normal random mutation, it could not be controlled or eliminated. It would therefore survive and would proceed to interact with its complementary antigen, the normal thyroid cell, without prior antigenic stimulation. These suggestions would be consistent with the results of the age-specific incidence rates showing a random appearance of the disorder in the preselected population. After the initial appearance of the clone which has so escaped elimination, it is conceivable that contact with its complementary antigen might stimulate the replication of that specific clone of lymphocytes.

There is now considerable evidence for two distinct populations of lymphocytes necessary for immune response.[52] These include a thymic-dependent T-lymphocyte and a thymic-independent (bursa-equivalent) B-lymphocyte. The B-lymphocyte is probably represented by the gut lymphocyte in mammals. Present evidence suggests that the T-lymphocyte, which produces no circulating antibodies, may be linked to organ-specific autoimmune disease. This T-lymphocyte (which is essential for the delayed hypersensitivity response) has the additional propensity for stimulating B-lymphocytes which in turn do produce circulating immunoglobulin after the specific T-lymphocyte has been stimulated.[52]

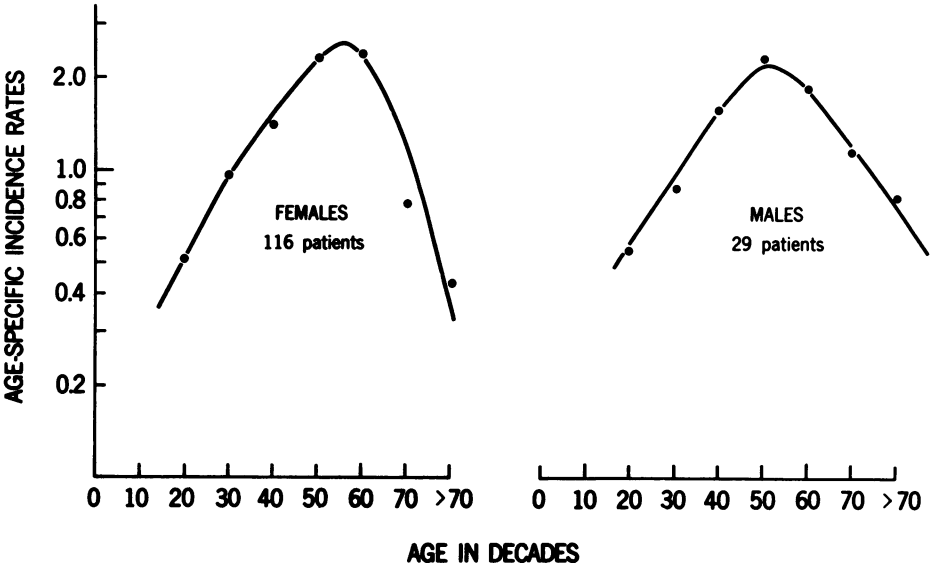

FIG. 1—Age-specific incidence rates for Hashimoto's thyroiditis in Toronto. Note that the curve for the male patients is broader than that for the females. This is almost certainly due to the small male sample.

It would seem plausible that the T-lymphocytes may arise in the manner described above, and then interact with the thyroid cells by means of a delayed hypersensitivity response. In addition, the T-lymphocytes so interacting might variably stimulate the B-lymphocytes to produce thyroid autoantibodies. Since groups of B-lymphocytes would likely be stimulated, the thyroid antibodies would be expected to be polyclonal, which indeed they are.[53]

Such a theory might also explain the close association between Hashimoto's disease, Graves' disease and pernicious anemia.[31] These disorders tend to occur in the same patients and their families. The appearance of these diseases may depend upon two variables: the extent of the inherited defect in immunological surveillance (with respect to one specific clone or a few closely related clones of lymphocytes) and the chance mutation of the appropriate clone. One might have a large defect in immunological surveillance, so that one could not eliminate the clone for either Hashimoto's disease or pernicious anemia, but if those particular clones did not arise by random mutation during the lifespan of that person, then neither disease would develop. It is evident, however, from an inspection of the age-specific incidence rates, that during the normal lifespan, penetrance of the disease approaches unity. Therefore most persons prone genetically to develop such a disease will ultimately contract it.

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